```
=> s insulin(P)(aspartyl)
           1   FILE ADISCTI
           0*  FILE ADISNEWS
           1   FILE AGRICOLA
           0*  FILE BIOCOMMERCE
          34   FILE BIOSIS
           3*  FILE BIOTECHABS
           3*  FILE BIOTECHDS
           8*  FILE BIOTECHNO
           4   FILE CABA
           5   FILE CANCERLIT
          42   FILE CAPLUS
           0*  FILE CEABA-VTB
           0*  FILE CIN
           4   FILE DISSABS
           1   FILE DDFU
          21   FILE DGENE
           3   FILE DRUGU
          19   FILE EMBASE
          13*  FILE ESBIOBASE
           3*  FILE FEDRIP
           0*  FILE FOMAD
           0*  FILE FOREGE
           0*  FILE FROSTI
           1*  FILE FSTA
          22   FILE IFIPAT
           2   FILE JICST-EPLUS
           0*  FILE KOSMET
           7   FILE LIFESCI
           0*  FILE MEDICONF
          22   FILE MEDLINE
           0*  FILE NTIS
           0*  FILE NUTRACEUT
           7*  FILE PASCAL
  53 FILES SEARCHED...
           0*  FILE PHARMAML
          20   FILE SCISEARCH
          25   FILE TOXCENTER
          50   FILE USPATFULL
           3   FILE USPAT2
          15   FILE WPIDS
          15   FILE WPINDEX

  28 FILES HAVE ONE OR MORE ANSWERS,    68 FILES SEARCHED IN STNINDEX

L1    QUE INSULIN(P)(ASPARTYL)
```

```
=> s lithocholyl(P)insulin
L9          29 LITHOCHOLYL(P) INSULIN

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10          28 DUP REM L9 (1 DUPLICATE REMOVED)

=> d bib, hit 1-

YOU HAVE REQUESTED DATA FROM 28 ANSWERS - CONTINUE? Y/(N):y


L10  ANSWER 1 OF 28  USPATFULL on STN
AN    2004:7761  USPATFULL
TI    Novel formulations
IN    Langkjaer, Liselotte, Holte, DENMARK
PI    US 2004006000      A1   20040108
AI    US 2003-429508     A1   20030505 (10)
PRAI  DK 2002-683         20020507
DT    Utility
FS    APPLICATION
LREP  Reza Green, Esq., Novo Nordisk Pharmaceuticals, Inc., 100 College Road
      West, Princeton, NJ, 08540
CLMN  Number of Claims: 34
ECL   Exemplary Claim: 1
DRWN  No Drawings
LN.CNT 780
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM  [0053] In a preferred embodiment of this invention, the soluble acylated
      insulin analogue is insulin detemir
      (Lys.sup.B29(N.sup.ε-tetradecanoyl) des( B30) human
      insulin). In a further preferred embodiment of this invention,
      the acylated insulin is Lys.sup.B29(N.sup.ε-
      hexadecanoyl) des(B30) human insulin;
      Lys.sup.B29(N.sup.ε-tetradecanoyl) human  insulin;
      Lys.sup.B29(N.sup.ε-hexadecanoyl) human  insulin;
      Lys.sup.B28 (N.sup.ε-tetradecanoyl) Lys.sup.B28 Pro.sup.B29
      human insulin; Lys.sup.B28(N.sup.ε-hexadecanoyl)
      Lys.sup.B28Pro.sup.B29 human insulin;
      Lys.sup.B30(N.sup.ε-tetradecanoyl) Thr.sup.B29Lys.sup.B30 human
      insulin; Lys.sup.B30(N.sup.ε-hexadecanoyl)
      Thr.sup.B29Lys.sup.B30 human insulin;
      Lys.sup.B29(N.sup.ε-(N-hexadecanoyl-γ-glutamyl)) des(B30)
      human insulin; Lys.sup.B29(N.sup.ε-(N-
      lithocholyl-γ-glutamyl)) des(B30) human  insulin;
      Lys.sup.B29(N.sup.ε-(ω-carboxyheptadecanoyl)) des(B30)
      human insulin; or Lys.sup.B29(N.sup.ε-(ω-
      carboxyheptadecanoyl)) human insulin.


L10  ANSWER 2 OF 28  USPATFULL on STN
AN    2004:7760  USPATFULL
TI    Polyamino acid-based particle insulin preparation
IN    Andreasen, Kasper Huus, Kobenhavn V, DENMARK
      Balschmidt, Per, Espergaerde, DENMARK
      Kimer, Lone, Farum, DENMARK
PI    US 2004005999      A1   20040108
AI    US 2003-384105     A1   20030307 (10)
PRAI  DK 2002-349         20020307
      US 2002-363136P     20020308 (60)
DT    Utility
```

FS APPLICATION
LREP Reza Green, Esq., Novo Nordisk Pharmaceuticals, Inc., 100 College Road West, Princeton, NJ, 08540
CLMN Number of Claims: 39
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 603
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0020] In some embodiments, the **insulin** derivative is a derivative of human **insulin** having one or more lipophilic substituents, including, without limitation, B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(co-carboxyheptadecanoyl)-des(B30) human **insulin**, and B29-N.sup.ε-(ω)-carboxyheptadecanoyl) human **insulin**.

SUMM [0047] In another embodiment the **insulin** derivative is selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl LyS.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl LyS.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω)-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω)-carboxyheptadecanoyl) human **insulin**.

CLM What is claimed is:
32. A pharmaceutical preparation according to claim 31, wherein the **insulin** derivative is selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl**-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(co-carboxyheptadecanoyl)-des(B30) human **insulin**, and B29-N.sup.ε-(co)-carboxyheptadecanoyl) human **insulin**.

L10 ANSWER 3 OF 28 USPATFULL on STN
AN 2003:335394 USPATFULL
TI Method and composition for treatment of diabetes, hypertension, chronic heart failure and fluid retentive states
IN Carr, Richard David, Vaerlose, DENMARK
PI US 2003236272 A1 20031225
AI US 2003-421465 A1 20030423 (10)
RLI Continuation of Ser. No. WO 2003-DK17, filed on 13 Jan 2003, UNKNOWN
PRAI DK 2002-47 20020111
US 2002-348332P 20020114 (60)
DT Utility
FS APPLICATION
LREP Reza Green, Esq., Novo Nordisk Pharmaceuticals, Inc., 100 College Road West, Princeton, NJ, 08540
CLMN Number of Claims: 23
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2768
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0041] In one preferred embodiment the derivative is human **insulin** or an analogue thereof containing a C.sub.6 to C.sub.40 lipophilic substituent in position B29. Preferably, the derivative may be selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω-carboxyheptadecanoyl) human **insulin**.

L10 ANSWER 4 OF 28 USPATFULL on STN
AN 2003:325138 USPATFULL
TI Novel ligands for the hisb10 zn2+ sites of the r-state insulin hexamer
IN Olsen, Helle Birk, Allerod, DENMARK
kaarsholm, Niels C., Vanlose, DENMARK
Madsen, Peter, Bagsvaerd, DENMARK
Ostergaard, Soren, Bronshoj, DENMARK
Ludvigsen, Svend, Lynge, DENMARK
Jakobsen, Palle, Vaerlose, DENMARK
Petersen, Anders Klarskov, Naerum, DENMARK
Steensgaard, Dorte Bjerre, Kobenhavn, DENMARK
PI US 2003229120 A1 20031211
AI US 2003-332541 A1 20030514 (10)
WO 2002-DK595 20020913
PRAI DK 2001-1337 20010914
DK 2002-1066 20020705
DT Utility
FS APPLICATION
LREP NOVO NORDISK OF NORTH AMERICA, INC, 405 LEXINGTON AVENUE, SUITE 6400, NEW YORK, NY, 10017
CLMN Number of Claims: 204
ECL Exemplary Claim: 1
DRWN 5 Drawing Page(s)

LN.CNT 8154
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0010] Most recently, a series of soluble **insulin** derivatives with a hydrophobic moiety covalently attached to the side chain of Lys.sup.B29 have been synthesized. These derivatives may show prolonged action profile due to various mechanisms including albumin binding (e.g. B29-N.sup.ε-myristoyl-des(B30) human **insulin**), extensive protein self-association and/or stickiness (e.g. B29-N.sup.ε-(N- **lithocholyl**-γ-glutamyl)-des(B30) human **insulin**) induced by the attached hydrophobic group.

DETD [0339] In another embodiment the **insulin** derivative is selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω-carboxyheptadecanoyl) human **insulin**.

DETD [0706] In another embodiment of the invention the **insulin** derivative is selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω-carboxyheptadecanoyl) human **insulin**.

CLM What is claimed is:

195. An R-state **insulin** hexamer according to claim 194 wherein the **insulin** derivative is selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl LYS.sup.B28Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω-carboxyheptadecanoyl) human **insulin**.

L10 ANSWER 5 OF 28 USPATFULL on STN
AN 2003:300750 USPATFULL
TI Polyamino acid-based particle insulin formulation
IN Andreasen, Kasper Huus, Kobenhavn V, DENMARK
Kimer, Lone, Farum, DENMARK
PI US 2003211976 A1 20031113
AI US 2003-383917 A1 20030307 (10)
PRAI DK 2002-350 20020307
US 2002-363135P 20020308 (60)
DT Utility
FS APPLICATION
LREP Reza Green, Esq., Novo Nordisk Pharmaceuticals, Inc., 100 College Road West, Princeton, NJ, 08540
CLMN Number of Claims: 38
ECL Exemplary Claim: 1
DRWN 3 Drawing Page(s)
LN.CNT 674
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0022] In some embodiments, the **insulin** derivative is a derivative of human **insulin** having one or more lipophilic substituents, including, without limitation, B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sub.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin**, and B29-N.sup.ε-(ω-carboxyheptadecanoyl) human **insulin**.

L10 ANSWER 6 OF 28 USPATFULL on STN
AN 2003:226277 USPATFULL
TI Renin-angiotensin system in diabetes mellitus
IN Pedersen-Bjergaard, Ulrik, Hillerod, DENMARK
Agerholm-Larsen, Birgit, Birkerod, DENMARK
Thorsteinsson, Birger, Hellerup, DENMARK
Pramming, Stig, Copenhagen K, DENMARK
PI US 2003158090 A1 20030821
AI US 2002-195330 A1 20021004 (10)
PRAI US 2001-306859P 20010723 (60)
DT Utility
FS APPLICATION
LREP JACOBSON HOLMAN PLLC, 400 SEVENTH STREET N.W., SUITE 600, WASHINGTON, DC, 20004
CLMN Number of Claims: 60
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1605
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD [0065] In one preferred embodiment the derivative is human **insulin** or an analogue thereof containing a C.sub.6 to C.sub.40 lipophilic substituent in position B29. Preferably, the derivative may be selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30)

human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω-carboxyheptadecanoyl) human **insulin**.

CLM What is claimed is:

10. The method according to claim 6, wherein the derivative is selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω-carboxyheptadecanoyl) human **insulin**.

56. The method according to claim 51, wherein the derivative is selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω-carboxyheptadecanoyl) human **insulin**.

L10 ANSWER 7 OF 28 USPATFULL on STN
AN 2003:4057 USPATFULL
TI Zinc-free and low-zinc insulin preparations having improved stability
IN Boderke, Peter, Frankfurt am Main, GERMANY, FEDERAL REPUBLIC OF
PI US 2003004096 A1 20030102
AI US 2002-102862 A1 20020322 (10)
PRAI DE 2001-114178 20010323
DT Utility
FS APPLICATION
LREP Finnegan, Henderson, Farabow,, Garrett & Dunner, L.L.P., 1300 I Street, N.W., Washington, DC, 20005-3315
CLMN Number of Claims: 29
ECL Exemplary Claim: 1

DRWN No Drawings
LN.CNT 723
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0036] In some embodiments, the polypeptide of the preparation is an **insulin** occurring in nature, for example human, bovine or porcine **insulin**, or the **insulin** of another animal or mammal. In some embodiments, the polypeptide of the preparation comprises an **insulin** analog, selected from at least one of Gly(A21)-Arg(B31)-Arg(B32) human **insulin**; Lys(B3)-Glu(B29) human **insulin**; Lys.sup.B28Pro.sup.B29 human **insulin**, B28 Asp human **insulin**, human **insulin**, in which proline in position B28 has been substituted by Asp, Lys, Leu, Val or Ala and where in position B29 Lys can be substituted by Pro; AlaB26 human **insulin**; des(B28-B30) human **insulin**; des(B27) human **insulin** or des(B30) human **insulin**. In additional embodiments, the polypeptide of the preparation comprises an **insulin** derivative selected from at least one of B29-N-myristoyl-des(B30) human **insulin**, B29-N-palmitoyl-des(B30) human **insulin**, B29-N-myristoyl human **insulin** , B29-N-palmitoyl human **insulin**, B28-N-myristoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B28-N-palmitoyl-Lys.sup.B28Pro.sup.B29 human **insulin**, B30-N-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N-(N-**lithocholyl**-Y-glutamyl)-des(B30) human **insulin** , B29-N-(ω-carboxyheptadecanoyl)-des(B30) human **insulin**, and B29-N-(ω-carboxyheptadecanoyl) human **insulin**. In some embodiments, the polypeptide may comprise an active **insulin** metabolite. Some embodiments comprise preparations containing mixtures of one or more of an **insulin**, an **insulin** analog, an **insulin** derivative, and an active **insulin** metabolite, for example, selected from those described above.

CLM What is claimed is:
18. The formulation as claimed in claim 1, wherein the **insulin** derivative is selected from at least one of B29-N-myristoyl-des(B30) human **insulin**; B29-N-palmitoyl-des(B30) human **insulin** ; B29-N-myristoyl human **insulin**; B29-N-palmitoyl human **insulin**; B28-N-myristoyl Lys.sup.B28Pro.sup.B29 human **insulin**; B28-N-palmitoyl-Lys.sup.B28Pro.sup.B29 human **insulin**; B30-N-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**; B30-N-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**; B29-N-(N-palmitoyl-γ-glutamyl)-des(B39) human **insulin**; B29-N-(N-**lithocholyl**-γ-glutamyl)-des(B30) human **insulin**; B29-N-(ω-carboxyheptadecanoyl)-des(B30) human **insulin**; and B29-N-(ω-carboxyheptadecanoyl) human **insulin**.

L10 ANSWER 8 OF 28 USPATFULL on STN
AN 2003:279178 USPATFULL
TI Insulin preparations for pulmonary delivery containing menthol
IN Havelund, Svend, Bagsv.ae butted.rd, DENMARK
PA Novo Nordisk A/S, Bagsvaerd, DENMARK (non-U.S. corporation)
PI US 6635617 B1 20031021
AI US 1999-418778 19991015 (9)
PRAI DK 1998-1326 19981016
US 1998-106018P 19981028 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Low, Christopher S. F.; Assistant Examiner: Lukton,

David
LREP Green, Reza
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 515
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM The **insulin** derivative according to this embodiment is preferably selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N-**lithocholyl**-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω-carboxyheptadecanoyl) human **insulin**.

SUMM The most preferred **insulin** derivative is B29-N.sup.ε-myristoyl-des(B30) human **insulin** or B29-N.sup.ε-(N-**lithocholyl**-γ-glutamyl)-des(B30) human **insulin**.

CLM What is claimed is:
17. The **insulin** formulation according to claim 13, wherein the **insulin** derivative is selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω-carboxyheptadecanoyl) human **insulin**.

18. The **insulin** formulation according to claim 17, wherein the **insulin** derivative is B29-N.sup.ε-myristoyl-des(B30) human **insulin** or B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**.

L10 ANSWER 9 OF 28 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-441045 [41] WPIDS
DNC C2003-116552
TI New zinc binding ligands useful in R-state insulin hexamer, in the treatment of diabetes.
DC B04 B05
IN JAKOBSEN, P; KAARSHOLM, N C; LUDVIGSEN, S; MADSEN, P; OLSEN, H B; OSTERGAARD, S; PETERSEN, A K; STEENSGAARD, D B
PA (JAKO-I) JAKOBSEN P; (KAAR-I) KAARSHOLM N C; (LUDV-I) LUDVIGSEN S;

(MADS-I) MADSEN P; (OLSE-I) OLSEN H B; (OSTE-I) OSTERGAARD S; (PETE-I) PETERSEN A K; (STEE-I) STEENSGAARD D B; (NOVO) NOVO NORDISK AS

CYC 101

PI WO 2003027081 A2 20030403 (200341)* EN 172p
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2003229120 A1 20031211 (200382)

ADT WO 2003027081 A2 WO 2002-DK595 20020913; US 2003229120 A1 WO 2002-DK595 20020913, US 2003-332541 20030514

PRAI US 2002-396051P 20020710; DK 2001-1337 20010914; US 2001-323925P 20010921; DK 2002-1066 20020705

TECH UPTX: 20040115

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (Claimed): Preparation of (I) involves:
(a) identifying starter compound that are able to displace a ligand from the R-state His-B10-Zn2+ site;
(b) optionally attaching a fragment containing 0-5 neutral alpha- or beta-amino acids; and
(c) attaching a fragment containing 1-20 positively charged amino or guanidino groups.
Preferred Components: The **insulin** hexamer further comprises at least 3 phenolic molecules. The **insulin** is human **insulin**, its analog and/or derivative. The **insulin** analog is an analog (where position B28 is Asp, Lys, Leu, Val or Ala (preferably Asp or Lys) and position B29 is Lys or Pro), and des (B28 - B30), des (B27) or des (B30) human **insulin** (preferably des (B30) human **insulin**). The derivative of human **insulin** has at least one lipophilic substituent (preferably B29-Nepsilon-myristoyl-des(B30) human **insulin**, B29-Nepsilon-palmitoyl-des(B30) human **insulin**, B29-Nepsilon-myristoyl-human **insulin**, B29-Nepsilon-palmitoyl-human **insulin**, B28-Nepsilon-myristoyl-Lys-B28 Pro-B29 human **insulin**, B28-Nepsilon-palmitoyl-Lys-B28 Pro-B29 human **insulin**, B30-Nepsilon-myristoyl-Thr-B29 Lys-B30 human **insulin**, B30-Nepsilon-palmitoyl-Thr-B29 Lys-B30 human **insulin**, B29-Nepsilon-(N-palmitoyl-gamma-glutamyl)-des(B30)-human **insulin**, B29-Nepsilon-(N-**lithocholyl**-gamma-glutamyl)-des(B30)-human **insulin**, B29-Nepsilon-(omega-carboxyheptadecanoyl)-des(B30)-human **insulin**, and B29-Nepsilon-(omega-carboxyheptadecanoyl)-human **insulin**, especially B29-Nepsilon-myristoyl-des(B30) human **insulin**). The ratio of precipitated **insulin** and dissolved **insulin** is 99:1-1:99 (preferably 70:30-30:70).

L10 ANSWER 10 OF 28 USPATFULL on STN

AN 2002:344410 USPATFULL

TI Pulmonary insulin crystals

IN Havelund, Svend, Bagsvaerd, DENMARK

PI US 2002198140 A1 20021226

AI US 2002-152535 A1 20020520 (10)

RLI Continuation of Ser. No. US 2001-836496, filed on 17 Apr 2001, ABANDONED
Continuation of Ser. No. US 1998-45038, filed on 20 Mar 1998, GRANTED, Pat. No. US 6310038

PRAI DK 1997-317 19970320
US 1997-41390P 19970327 (60)

DT Utility

FS APPLICATION

LREP Steve T. Zelson, Esq., Novo Nordisk of North America, Inc., Suite 6400,

405 Lexington Avenue, New York, NY, 10174-6400
CLMN Number of Claims: 28
ECL Exemplary Claim: 1
DRWN 1 Drawing Page(s)
LN.CNT 488
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0029] In another preferred embodiment the **insulin** used is an **insulin** derivative, preferably selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B28-N.sub.ε-palmitoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.30 human **insulin**, B29-N.sup.68-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω-carboxyheptadecanoyl) human **insulin**, more preferably Lys.sup.B29(N-ε acylated) des(B30) human **insulin**.

CLM What is claimed is:
8. Zinc free **insulin** crystals according to any one claims 1 to 4, wherein the **insulin** is an **insulin** derivative, preferably selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28Pro.sub.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N-**lithocholyl**-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω-carboxyheptadecanoyl) human **insulin**.

28. A method of treating diabetes mellitus comprising administering by pulmonary delivery to a person in need of such treatment an effective amount of an **insulin** derivative having a protracted onset of action, preferably selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω-carboxyheptadecanoyl)

human **insulin**.

L10 ANSWER 11 OF 28 USPATFULL on STN
AN 2002:280549 USPATFULL
TI Aggregates of human insulin derivatives
IN Havelund, Svend, Bagsvaerd, DENMARK
Jonassen, Ib, Valby, DENMARK
Balschmidt, Per, Espergaerde, DENMARK
Hoeg-Jensen, Thomas, Klampenborg, DENMARK
PI US 2002155994 A1 20021024
AI US 2002-83058 A1 20020225 (10)
RLI Continuation of Ser. No. US 1999-227774, filed on 8 Jan 1999, PENDING Continuation-in-part of Ser. No. US 1998-193552, filed on 17 Nov 1998, ABANDONED Continuation of Ser. No. WO 1998-DK461, filed on 23 Oct 1998, UNKNOWN
PRAI DK 1997-1218 19971024
DT Utility
FS APPLICATION
LREP Reza Green, Esq., Novo Nordisk of North America, Inc., Suite 6400, 405 Lexington Avenue, New York, NY, 10174-6401
CLMN Number of Claims: 60
ECL Exemplary Claim: 1
DRWN 4 Drawing Page(s)
LN.CNT 770
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD [0067] Some of the derivatives listed in the aforementioned patent applications, and described in the publications of Markussen, Diabetologia 39, 281-288, 1996; Kurzhals, Biochem J. 312, 725-731, 1995; Kurzhals, J. Pharm Sciences 85, 304-308, 1996; and Whittingham, Biochemistry 36, 2826-2831, 1997 as being protracted due to the albumin binding mechanism, do also posses the ability to form high molecular weight soluble aggregates in accordance with the present invention. Lys.sup.B29(N.sup.ε **lithocholyl**-γ-Glu-) des(B30) human **insulin** from WO 95/07931 and Lys.sup.B29(N.sup.68 ω-carboxyheptadecanoyl-) des(B30) human **insulin** from WO 97/31022 are examples of **insulin** derivatives capable of forming high molecular weight soluble aggregates at neutral pH. There is selectivity between the lipophillic substituents in their ability to induce formation of aggregates. Thus, of the two isomers, LyS.sup.B29(N.sup.ε **lithocholyl**-γ-Glu-) des(B30) human **insulin** and LyS.sup.B29(N.sup.ε **lithocholyl**-α-Glu-) des(B30) human **insulin**, only the first forms aggregates in the formulation used, see Table 1.
DETD [0076] K.sub.AV values, albumin binding constants and disappearance half-times for associating **insulin** derivatives larger than aldolase (Mw 158 kDa), non-associating **insulin** derivatives smaller than aldolase and standards used as markers of molecular size. Albumin binding constants and disappearance half times in pigs have been normalised using LyS.sup.B29(N.sup.ε tetradecanoyl) des(B30) human **insulin** as the reference compound. Disappearance T.sub.50% for NPH **insulin** in pigs have been measured to 10.5 h (Markussen et al. 1996).

Compounds	Albumin binding K.sub.AV (mol/l).sup.-1	Disappearance K.sub.ass, T.sub.50%, h
Associating derivatives of		

human **insulin** forming
aggregates larger than aldolase.**
Lys.sup.B29(N.sup.ε **lithocholyl**-γ-Glu-) des(B30) 0.04*
0.3 + 10.sup.5 22.8
Lys.sup.B29(N.sup.ε ω-carboxyheptadecanoyl) des(B30) 0.05 25
+ 10.sup.5 18.7
Lys.sup.B29(N.sup.ε ω-carboxynonadecanoyl) des(B30) 0.04 36
+ 10.sup.5 21.9
Lys.sup.B29(N.sup.ε cholesteryloxycarbonyl) 0 00
Non-associating derivatives of
human **insulin** forming aggregates
smaller than aldolase.**
Human **insulin***** 0.61 0
(2)
Human **insulin** (Zinc free) 0.72
Lys.sup.B29(N.sup.ε **lithocholyl** (Zinc free) 0 74
Lys.sup.B29(N.sup.ε decanoyl) *** 0 67 0.06 +
10.sup.5 5.1
Lys.sup.B29(N.sup.ε tetradecanoyl) des(B30) 0.51 1.0 +
10.sup.5 14.3
Lys.sup.B29(N.sup.ε **lithocholyl**-α-Glu-) des(B30) 0.53
0.3 + 10.sup.5 11.8
Standards.****
B9Asp, B27Glu human **insulin** (monomeric, Mw 6 kDa) 0.71 0
(1)
Ribonuclease (Mw 13.7 kDa) 0.63
Albumin (Mw 67 kDa) 0.38
Aldolase (Mw 158 kDa) 0.32
Catalase (Mw 232 kDa) 0.30
Ferritin (Mw 440 kDa) 0.19
Thyroglobulin (Mw 669 kDa) 0.08

*75% of the derivatives eluted in the main peak, and 25% in the position of the monomer or dimer.
**Applied 200 µl sample as a pharmaceutical preparation comprising 600 µM of derivative , 200 µM Zn.sup.2+, 0-20 mM sodium chloride, 7 mM sodium phosphate, 16 mM phenol, 16 mM m-cresol, 1.6% glycerol and pH of 7.5
***Same as ** but 300 µM Zn.sup.2+.
****Standards applied dissolved in water.
DETD [0077] Examples of **insulin** derivatives capable of forming soluble high molecular weight aggregates and having a protracted action based primarily on this property are Lys.sup.B29(N.sup.ε **lithocholyl**-γ-Glu-) des(B30) human **insulin**, see Table 1. Notably, the ratio between disappearance half time and albumin binding constant is high for this class of compounds. Examples of **insulin** derivatives incapable of forming soluble high molecular weight aggregates but having a protracted action based on the albumin binding property are Lys.sup.B29(N.sup.ε **lithocholyl** -α-Glu-) des(B30) human **insulin** and Lys.sup.B29(N.sup.ε-tetradecanoyl-) des(B30) human **insulin**, see Table 1. Notably, the ratio between disappearance half time/albumin binding constant is low for this class of compounds.

L10 ANSWER 12 OF 28 USPATFULL on STN
AN 2002:48575 USPATFULL
TI Glucose dependent release of insulin from glucose sensing insulin derivatives
IN Jensen, Thomas Hoeg, Klampenborg, DENMARK
Havelund, Svend, Bagsvaerd, DENMARK
Markussen, Jan, Herlev, DENMARK
Ostergaard, Soren, Bronshoj, DENMARK

Ridderberg, Signe, Lyngby, DENMARK
Balschmidt, Per, Espergaerde, DENMARK
Schaffer, Lauge, Copenhagen, DENMARK
Jonassen, Ib, Valby, DENMARK
PI US 2002028767 A1 20020307
AI US 2001-870884 A1 20010531 (9)
PRAI DK 2000-20000858 20000602
US 2000-213375P 20000623 (60)
DT Utility
FS APPLICATION
LREP Reza Green, Esq., Novo Nordisk of North America, Inc., Suite 6400, 405 Lexington Avenue, New York, NY, 10174-6401
CLMN Number of Claims: 28
ECL Exemplary Claim: 1
DRWN 4 Drawing Page(s)
LN.CNT 1467
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD [0061] Some of the derivatives listed in the aforementioned patent applications, and described in the publications of Markussen, Diabetologia 39, 281-288, 1996; Kurzhals, Biochem J. 312, 725-731, 1995; Kurzhals, J. Pharm Sciences 85, 304-308, 1996; and Whittingham, Biochemistry 36, 2826-2831, 1997 as being protracted due to the albumin binding mechanism, do also posses the ability to form high molecular weight soluble aggregates. Lys.sup.B29 (N.sup.ε-**lithocholyl**-γ-glutamyl) des(B30) human **insulin** from WO 95107931 and Lys.sup.B29(N.sup.εω-carboxyheptadecanoyl) des(B30) human **insulin** from WO 97/31022 are examples of **insulin** derivatives capable of forming high molecular weight soluble aggregates at neutral pH.
DETD [0110] 4-Methyl-aminomethyl-3-borono-benzoic acid (Combi-Blocks, San Diego, Calif., USA) was N-acylated using N-hydroxysuccinimidyl lithocholate as acylating agent. The resulting **lithocholyl** benzoic acid was converted to its N-hydroxysuccinimidyl ester and used to selectively acylate the ε-amino group of LysB29 in des(B30) human **insulin** (U.S. Pat. No. 15 5,646,242) to give structure 11. ##STR12##

L10 ANSWER 13 OF 28 USPATFULL on STN
AN 2002:317402 USPATFULL
TI Stable aqueous insulin preparations without phenol and cresol
IN Havelund, Svend, Bagsv.ae butted.rd, DENMARK
Kaarsholm, Niels C., Vanl.o slashed.se, DENMARK
PA Novo Nordisk A/S, Bagsvaerd, DENMARK (non-U.S. corporation)
PI US 6489292 B1 20021203
AI US 1999-441702 19991116 (9)
PRAI DK 1998-1506 19981118
US 1998-110707P 19981203 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Low, Christopher S. F.; Assistant Examiner: Mohamed, Abdel A.
LREP Green, Esq., Reza
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 503
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM The **insulin** derivative according to this embodiment is preferably selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human

insulin, B28-N.sup.ε-myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl -Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω-carboxyheptadecanoyl) human **insulin**.

SUMM The most preferred **insulin** derivative is B29-N.sup.ε-myristoyl-des(B30) human **insulin** or B29-N.sup.ε-(N-**lithocholyl**-γ-glutamyl)-des(B30) human **insulin**.

CLM What is claimed is:
20. An **insulin** preparation according to claim 19, wherein the **insulin** derivative is selected from the group consisting of B29-N.sup.ε-myristoyl-des(B30) human **insulin**, B29-N.sup.ε-palmitoyl-des(B30) human **insulin**, B29-N.sup.ε-myristoyl human **insulin**, B29-N.sup.ε-palmitoyl human **insulin**, B28-N.sup.ε-myristoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B28-N.sup.ε-palmitoyl Lys.sup.B28Pro.sup.B29 human **insulin**, B30-N.sup.ε-myristoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B30-N.sup.ε-palmitoyl-Thr.sup.B29Lys.sup.B30 human **insulin**, B29-N.sup.ε-(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε-(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε-(ω-carboxyheptadecanoyl) human **insulin**.

21. An **insulin** preparation according to claim 20 wherein the **insulin** derivative is B29-N.sup.ε-myristoyl-des(B30) human **insulin** or B29-N.sup.ε-(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**.

L10 ANSWER 14 OF 28 USPATFULL on STN
AN 2002:238991 USPATFULL
TI Aggregates of human insulin derivatives
IN Havelund, Svend, Bagsv.ae butted.rd, DENMARK
Jonassen, Ib, Valby, DENMARK
Balschmidt, Per, Esperg.ae butted.rde, DENMARK
H.o slashed.eg-Jensen, Thomas, Klampenborg, DENMARK
PA Novo Nordisk A/S, Bagsvaerd, DENMARK (non-U.S. corporation)
PI US 6451762 B1 20020917
AI US 1999-227774 19990108 (9)
RLI Continuation-in-part of Ser. No. US 1998-193552, filed on 17 Nov 1998
Continuation of Ser. No. WO 1998-DK461, filed on 23 Oct 1998
PRAI DK 1997-1218 19971024
US 1997-64170P 19971124 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Low, Christopher S. F.; Assistant Examiner: Gupta, Anish
LREP Reza Green, Esq., Bork, Esq., Richard W.
CLMN Number of Claims: 3
ECL Exemplary Claim: 1

DRWN 4 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 591
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD Some of the derivatives listed in the aforementioned patent applications, and described in the publications of Markussen, Diabetologia 39, 281-288, 1996; Kurzhals, Biochem J. 312, 725-731, 1995; Kurzhals, J. Pharm Sciences 85, 304-308, 1996; and Whittingham, Biochemistry 36, 2826-2831, 1997 as being protracted due to the albumin binding mechanism, do also posses the ability to form high molecular weight soluble aggregates in accordance with the present invention. Ly B.sup.29(N.sup.ε **lithocholyl**-γ-Glu-) des(B30) human **insulin** from WO 95/07931 and Ly.sup.B29(N.sup.εω-carboxyheptadecanoyl-) des(B30) human **insulin** from WO 97/31022 are examples of **insulin** derivatives capable of forming high molecular weight soluble aggregates at neutral pH. There is selectivity between the lipophillic substituents in their ability to induce formation of aggregates. Thus, of the two isomers, Lys.sup.B29(N.sup.ε **lithocholyl**-γ-Glu-) des(B30) human **insulin** and Lys.sup.B29(N.sup.ε **lithocholyl**-α-Glu-) des(B30) human **insulin**, only the first forms aggregates in the formulation used, see Table 1.
DETD

Compounds	Albumin binding K.sub.ass, K.sub.AV (mol/l).sup.-1	Disappearance T.sub.50% h	
Associating derivatives of human **insulin** forming aggregates larger than aldolase.**			
Lys.sup.B29(N.sup.ε **lithocholyl**-γ-Glu-) des(B30)	0.04*	0.3 + 10.sup.5	22.8
Lys.sup.B29(N.sup.ε ω-carboxyheptadecanoyl) des(B30)	0.05	25 + 10.sup.5	18.7
Lys.sup.B29(N.sup.ε ω-carboxynonadecanoyl) des(B30)	0.04	36 + 10.sup.5	21.9
Lys.sup.B29(N.sup.ε cholesteryloxycarbonyl)	0.00		
Non-associating derivatives of human **insulin** forming aggregates smaller than aldolase.**			
Human **insulin*****	0.61	0	(2)
Human **insulin** (Zinc free)	0.72		
Lys.sup.B29(N.sup.ε **lithocholyl** (Zinc free)	0.74		
Lys.sup.B29(N.sup.ε decanoyl)***	0.67	0.06 + 10.sup.5	5.1
Lys.sup.B29(N.sup.ε tetradecanoyl) des(B30)	0.51	1.0 + 10.sup.5	14.3
Lys.sup.B29(N.sup.ε **lithocholyl**-α-Glu-) des(B30)	0.53	0.3 + 10.sup.5	11.8
Standards.****			
B9Asp, B27Glu human **insulin** (monomeric, Mw 6 kDa)	0.71	0	(1)
Ribonuclease (Mw 13.7 kDa)	0.63		
Albumin (Mw 67 kDa)	0.38		
Aldolase (Mw 158 kDa)	0.32		
Catalase (Mw 232 kDa)	0.30		
Ferritin (Mw 440 kDa)	0.19		
Thyroglobulin (Mw 669 kDa)	0.08		

*75% of the derivatives eluted in the main peak, and 25% in the position of the monomer or dimer.
**Applied 200 µl sample as a pharmaceutical preparation comprising 600 µM of derivative, 200 µM Zn.sup.2+, 0-20 mM sodium chloride, 7 mM sodium phosphate, 16 mM phenol, 16 mM m-cresol, 1.6% glycerol and pH of 7.5.
***Same as ** but 300 µM Zn.sup.2+.
****Standards applied dissolved in water.
DETD Examples of **insulin** derivatives capable of forming soluble high molecular weight aggregates and having a protracted action based primarily on this property are Lys.sup.B29(N.sup.ε **lithocholyl**-γ-Glu-) des(B30) human **insulin**, see Table 1. Notably, the ratio between disappearance half time and albumin binding constant is high for this class of compounds. Examples of **insulin** derivatives incapable of forming soluble high molecular weight aggregates but having a protracted action based on the albumin binding property are Lys.sup.B29(N.sup.ε **lithocholyl** -α-Glu-) des(B30) human **insulin** and Lys.sup.B29 (N.sup.ε-tetradecanoyl-) des(B30) human **insulin**, see Table 1. Notably, the ratio between disappearance half time/albumin binding constant is low for this class of compounds.

L10 ANSWER 15 OF 28 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-156660 [15] WPIDS
DNC C2003-040601
TI New stable, zinc-free or low-zinc insulin formulation used for treating diabetes mellitus, comprises insulin, its analog, derivative or active metabolite, and stabilizing surfactant(s), e.g. polysorbate.
DC A96 B04 D16
IN BODERKE, P
PA (AVET) AVENTIS PHARMA DEUT GMBH; (BODE-I) BODERKE P
CYC 98
PI WO 2002076495 A1 20021003 (200315)* DE 30p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
DE 10114178 A1 20021010 (200315)
US 2003004096 A1 20030102 (200315)
NO 2003004125 A 20031111 (200381)
EP 1381385 A1 20040121 (200410) DE
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002076495 A1 WO 2002-EP2625 20020309; DE 10114178 A1 DE 2001-10114178 20010323; US 2003004096 A1 US 2002-102862 20020322; NO 2003004125 A WO 2002-EP2625 20020309, NO 2003-4125 20030916; EP 1381385 A1 EP 2002-729985 20020309, WO 2002-EP2625 20020309
FDT EP 1381385 A1 Based on WO 2002076495
PRAI DE 2001-10114178 20010323
TECH UPTX: 20030303
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preparation: (I) is prepared by combining the components in the form of aqueous solutions, adjusting the pH and making to up the final volume with water.
Preferred Active Agents: The **insulin** analog is Gly(A21), Arg(B31), Arg (B32)-human **insulin**, Lys(B3), Glu(B29)-human **insulin**, Asp(B28)-human **insulin**, Lys(B28), Pro(29)-human **insulin** or des(B30)-human **insulin**.
The **insulin** derivative is B29-N-myristoyl-des(B30)-human **insulin**, B29-N-palmitoyl-des(B30)-human **insulin**, B29-N-myristoyl-human **insulin**, B29-N-palmitoyl-human

insulin, B28-N-myristoyl-Lys(B28)-Pro(B29)-human **insulin**
, B28-N-palmitoyl-Lys(B28)-Pro(B29)-human **insulin**,
B30-N-myristoyl-Thr(B29)-Lys(B30)-human **insulin**,
B30-N-palmitoyl-Thr(B29)-Lys(B30)-human **insulin**,
B29-N-(N-palmitoyl-gamma-glutamyl)-des(B39)-human **insulin**,
B29-N-(N-**lithocholyl**-gamma-glutamyl)-des(B30)-human
insulin, B29-N-(omega-carboxy-heptadecanoyl)-des(B30)-human
insulin or B29-N-(omega-carboxyheptadecanoyl)-human
insulin.
Preferred Components: The surfactant is selected from alkali(ne earth) metal or amine soaps (preferably stearates, palmitates, oleates or ricinoleates); alkyl sulfates (preferably sodium lauryl sulfate, sodium cetyl or sodium stearyl sulfate); alkyl sulfonates; natural surfactants (preferably bile acid salts, saponins, gum arabic or lecithins); cationic surfactants (preferably alkonium halides, cetyl pyridinium chloride or Cetrimide (RTM)); fatty alcohols (preferably cetyl alcohol, stearyl alcohol or cholesterol (sic)); fatty acids; partial esters, fatty acid esters or ethers of glycerol, sorbitol or other polyols (preferably Span (RTM), Tween (RTM; polysorbate), Myrj (RTM), Brij (RTM), Triton (RTM) or Cremophor (RTM)); or polyols (preferably polypropylene glycols, poloxamers, Pluronics (RTM) or Tetronics (RTM).
The preservatives are phenol, cresol, chlorocresol, benzyl alcohol or parabens.
The isotonizing agents are mannitol, sorbitol, lactose, dextrose, trehalose, sodium chloride or glycerol.
The other additives are buffers (e.g. Tris, phosphate, citrate, acetate or glycylglycine), acids, alkalis, salts, protamine, arginine or Surfen (RTM).
Preferred Composition: (I) contains the **insulin** (or derivative, analog or metabolite) at 60-6000 (preferably 240-3000) nmol/ml; the surfactant at 0.1-10000 (preferably 1-1000) microg/ml; glycerol and/or mannitol at 100-250 mM; chloride at up to 150 mM; and buffer at 5-250 mM. (I) especially contains 3.5 mg/ml cresol, 3.5 mg/ml HMR 1964 (i.e. Lys(B3), Glu(B29)-human **insulin**), 6.0 mg/ml trometanol, 5.0 mg/ml sodium chloride and 0.1 mg/ml Tween 20 (RTM; polysorbate 20).

TECHNOLOGY FOCUS - POLYMERS - Preferred Materials: The surfactants include Span (RTM), Tween (RTM; polysorbate), Myrj (RTM), Brij (RTM), Triton (RTM), Cremophor (RTM), polypropylene glycols, poloxamers, Pluronics (RTM) or Tetronics (RTM).

L10 ANSWER 16 OF 28 USPATFULL on STN
AN 2001:191109 USPATFULL
TI Pulmonary insulin crystals
IN Havelund, Svend, Bagsvaerd, Denmark
PA Novo Nordisk A/S, Bagsvaerd, Denmark (non-U.S. corporation)
PI US 6310038 B1 20011030
AI US 1998-45038 19980320 (9)
PRAI DK 1997-317 19970320
US 1997-41390P 19970327 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Russel, Jeffrey E.
LREP Green, Esq., Reza
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 445
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD In another preferred embodiment the **insulin** used is an **insulin** derivative, preferably selected from the group consisting of B29-N.sup.ε -myristoyl-des(B30) human

insulin, B29-N.sup.ε -palmitoyl-des(B30) human **insulin**, B29-N.sup.ε -myristoyl human **insulin**, B29-N.sup.ε -palmitoyl human **insulin**, B28-N.sup.ε -myristoyl LyS.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε -palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε -myristoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B30-N.sup.ε -palmitoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B29-N.sup.ε -(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε -(N- **lithocholyl** -γ-glutamil)-des(B30) human **insulin**, B29-N.sup.ε -(ω-carboxyheptadecanoyl)des(B30) human **insulin** and B29-N.sup.ε -(ω-carboxyheptadecanoyl) human **insulin**, more preferably Lys.sup.B29 (N-ε acylated) des(B30) human **insulin**.

L10 ANSWER 17 OF 28 USPATFULL on STN
AN 2001:48018 USPATFULL
TI Stable concentrated insulin preparations for pulmonary delivery
IN Havelund, Svend, Bagsv.ae butted.rd, Denmark
PA Novo Nordisk A/S, Bagsvaerd, Denmark (non-U.S. corporation)
PI US 6211144 B1 20010403
AI US 1999-419668 19991015 (9)
PRAI US 1998-105986P 19981028 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Reamer, James H.
LREP Zelson, Esq., Steve T., Green, Esq., Reza
CLMN Number of Claims: 37
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 571
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM The **insulin** derivative according to this embodiment is preferably selected from the group consisting of B29-N.sup.ε -myristoyl-des(B30) human **insulin**, B29-N.sup.ε -palmitoyl-des(B30) human **insulin**, B29-N.sup.ε -myristoyl human **insulin**, B29-N.sup.ε -palmitoyl human **insulin**, B28-N.sup.ε -myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε -palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε -myristoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B30-N.sup.ε -palmitoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B29-N.sup.ε -(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε -(N-**lithocholyl**-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε -(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε -(ω-carboxyheptadecanoyl) human **insulin**.

SUMM The most preferred **insulin** derivative is B29-N.sup.ε -myristoyl-des(B30) human **insulin** or B29-N.sup.ε -(N-**lithocholyl**-γ-glutamyl)-des(B30) human **insulin**.

DETD 441 mg B29-N.sup.ε -(N- **lithocholyl**-γ-glutamyl)-des(B30) human **insulin** (143 nmol/mg) was suspended in 5 ml water at 0° C. and 220 μl 1 N NaOH added. After dissolution of the **insulin** analog 295 μl 0.1 M ZnCl.sub.2 was added and the solution stirred until a temporary precipitate was dissolved. 315 μl 0.32 mM phenol and 98 μl 0.5 M glycylglycine and 70 μl 1% Tween 20 were subsequently added and pH measured to 7.60. Finally 693 μl water was added and the solution was passed through a sterile 0.22

μm Millex®-GV filter unit to obtain 7 ml 9 mM B29-N.sup.ε -(N-lithocholy-γ-glutamyl)-des(B30) human **insulin**. The solution remained stable after 3 months at 5° C.

CLM What is claimed is:

17. An **insulin** preparation according to claim 16, wherein the **insulin** derivative is selected from the group consisting of B29-N.sup.ε -myristoyl-des(B30) human **insulin**, B29-N.sup.ε -palmitoyl-des(B30) human **insulin**, B29-N.sup.ε -myristoyl human **insulin**, B29-N.sup.ε -palmitoyl human **insulin**, B28-N.sup.ε -myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε -palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε -myristoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B30-N.sup.ε -palmitoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B29-N.sup.ε -(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε -(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε -(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε -(ω-carboxyheptadecanoyl) human **insulin**.

18. An **insulin** preparation according to claim 17, wherein the **insulin** derivative is B29-N.sup.ε -myristoyl-des(B30) human **insulin** or B29-N.sup.ε -(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**.

L10 ANSWER 18 OF 28 USPATFULL on STN
AN 2001:8023 USPATFULL
TI Stabilized insulin compositions
IN Langballe, Peter, Charlottenlund, Denmark
Norup, Elsebeth, Jyllinge, Denmark
PA Novo Nordisk A/S, Bagsvaerd, Denmark (non-U.S. corporation)
PI US 6174856 B1 20010116
AI US 1999-227053 19990107 (9)
PRAI EP 1998-610001 19980109
US 1998-71336P 19980114 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Moezie, F. T.
LREP Zelson, Esq., Steve T., Lambiris, Esq., Elia J.
CLMN Number of Claims: 19
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 654
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD The following are preferred **insulin** derivatives: N.sup.εB29 -myristoyl-des(B30) human **insulin**, N.sup.εB29 -palmitoyl-des(B30) human **insulin**, N.sup.εB29 -myristoyl human **insulin**, N.sup.εB29 -palmitoyl human **insulin**, N.sup.εB28 -myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, N.sup.εB28 -palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, N.sup.εB30 -myristoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, N.sup.εB30 -palmitoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, N.sup.εB29 -(N-palmitoyl-γ-glutamyl)-des (B30) human **insulin**, N.sup.εB29 -(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, N.sup.εB29 -(ω-carboxyheptadecanoyl)-des(B30) human **insulin**, and N.sup.εB29 -(ω-carboxyheptadecanoyl) human **insulin**

; the most preferred being N.sup.εB29 -myristoyl-des(B30) human **insulin**.

CLM What is claimed is:

13. The composition of claim 11, wherein the **insulin** derivative is selected from the group consisting of N.sup.εB29 -myristoyl-des(B30) human **insulin**, N.sup.εB29 -palmitoyl-des(B30) human **insulin**, N.sup.εB29 -myristoyl human **insulin**, N.sup.εB29 -palmitoyl human **insulin**, N.sup.εB28 -myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, N.sup.εB28 -palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, N.sup.εB30 -myristoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, N.sup.εB30 -palmitoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, N.sup.εB29 -(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, N.sup.εB29 -(N-**lithocholyl**-γ-glutamyl)-des(B30) human **insulin**, N.sup.εB29 (ω-carboxyheptadecanoyl)-des(B30) human **insulin**, and N.sup.εB29 -(ω-carboxyheptadecanoyl) human **insulin**.

15. The composition of claim 9, wherein the **insulin** derivative is selected from the group consisting of N.sup.εB29 -myristoyl-des(B30) human **insulin**, N.sup.εB29 -palmitoyl-des(B30) human **insulin**, N.sup.εB29 -myristoyl human **insulin**, N.sup.εB29 -palmitoyl human **insulin**, N.sup.εB28 -myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, N.sup.εB28 -palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, N.sup.εB30 -myristoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, N.sup.εB30 -palmitoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, N.sup.εB29 -(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, N.sup.εB29 -(N-**lithocholyl**-γ-glutamyl)-des(B30) human **insulin**, N.sup.εB29 -(ω-carboxyheptadecanoyl)-des(B30) human **insulin**, and N.sup.εB29 -(ω-carboxyheptadecanoyl) human **insulin**.

L10 ANSWER 19 OF 28 USPATFULL on STN
AN 2000:131806 USPATFULL
TI Methods for producing biphasic insulin formulations
IN Kimer, Lone L.o slashed.gstrup, Farum, Denmark
Balschmidt, Per, Esperg.ae butted.rde, Denmark
Jensen, Steen, Drag.o slashed.r, Denmark
PA Novo Nordisk A/S, Bagsvaerd, Denmark (non-U.S. corporation)
PI US 6127334 20001003
AI US 1998-198878 19981124 (9)
RLI Division of Ser. No. US 1997-879691, filed on 19 Jun 1997, now patented, Pat. No. US 5948751
PRAI DK 1996-684 19960620
DK 1996-899 19960827
US 1996-23264P 19960626 (60)
US 1996-24862P 19960828 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Lee, Howard C.
LREP Zelson, Esq., Steve T., Lambiris, Esq., Elias J.
CLMN Number of Claims: 23
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 746
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD B29-N.sup.ε -myristoyl-des(B30)-human **insulin**, B29-N.sup.ε -myristoyl human **insulin**, B29-N.sup.ε -palmitoyl human **insulin**, B28-N.sup.ε -myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε -palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε -myistoyl-Thr.sup.B29 -Lys.sup.B30 human **insulin**, B30-N.sup.ε -palmitoy-Thr.sup.B29 Lys.sup.B30 -human **insulin**, B29-N.sup.ε -(N-palmitoyl-γ-glutamyl)-des(B30)-human **insulin**, B29-N.sup.ε -(N- **lithocholyl** -γ-glutamyl)-des(B30)-human **insulin** and B29-N.sup.ε -(ω-carboxyheptadecanoyl)-des(B30)-human **insulin**; the most preferred being B29-N.sup.ε -myristoyl-des(B30)-human **insulin**.

L10 ANSWER 20 OF 28 USPATFULL on STN
AN 2000:37770 USPATFULL
TI Method for producing powder formulation comprising an insulin
IN Jensen, Steen, Drag.o slashed.r, Denmark
Hansen, Philip, Holte, Denmark
PA Novo Nordisk A/S, Bagsvaerd, Denmark (non-U.S. corporation)
PI US 6043214 20000328
AI US 1998-45397 19980320 (9)
PRAI DK 1997-318 19970320
US 1997-41644P 19970327 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Weddington, Kevin E.
LREP Zelson, Esq., Steven T., Lambiris, Esq., Elias J.
CLMN Number of Claims: 31
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 418
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM The **insulin** derivative is most preferably selected from the group consisting of B29-N.sup.ε -myristoyl-des(B30) human **insulin**, B29-N.sup.ε -palmitoyl-des(B30) human **insulin**, B29-N.sup.ε -myristoyl human **insulin**, B29-N.sup.ε -palmitoyl human **insulin**, B28-N.sup.ε -myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε -palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε -myristoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B30-N.sup.ε -palmitoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B29-N.sup.ε -(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε -(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε -(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε -(ω-carboxyheptadecanoyl) human **insulin**.

CLM What is claimed is:
26. The process of claim 1, wherein the **insulin** or analogue or derivative thereof is selected from the group consisting of B29-N.sup.ε -myristoyl-des(B30) human **insulin**, B29-N.sup.ε -palmitoyl-des(B30) human **insulin**, B29-N.sup.ε -myristoyl human **insulin**, B29-N.sup.ε -palmitoyl human **insulin**, B28-N.sup.ε -myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε -palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε -myristoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B30-N.sup.ε

-palmitoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B29-N.sup.ε -(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε -(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε -(ωcarboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε -(ω-carboxyheptadecanoyl) human **insulin**.

L10 ANSWER 21 OF 28 USPATFULL on STN
AN 2000:1850 USPATFULL
TI Acylated insulin
IN Havelund, Svend, Bagsvaerd, Denmark
Halstrom, John, Hundested, Denmark
Jonassen, Ib, Valby, Denmark
Andersen, Asser Sloth, Frederiksberg, Denmark
Markussen, Jan, Herlev, Denmark
PA Novo Nordisk A/S, Bagsvaerd, Denmark (non-U.S. corporation)
PI US 6011007 20000104
AI US 1997-975365 19971120 (8)
RLI Continuation-in-part of Ser. No. US 1995-400256, filed on 8 Mar 1995, now patented, Pat. No. US 5750497 which is a continuation-in-part of Ser. No. US 190829
PRAI DK 1993-1044 19930917
DT Utility
FS Granted
EXNAM Primary Examiner: Ulm, John; Assistant Examiner: Saoud, Christine
LREP Zelson, Esq., Steve T., Lambiris, Esq., Elias
CLMN Number of Claims: 115
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 3303
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD Synthesis of Lys.sup.B29 (N.sup.ε -[N.sup.α - **lithocholyl**-Glu(-)--OH]) des(B30) Human **Insulin**

L10 ANSWER 22 OF 28 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2000-387616 [33] WPIDS
DNC C2000-117636
TI New aqueous insulin formulations containing a non-phenolic stabilizer, useful for treating type I and type II diabetes, e.g. by pulmonary administration.
DC A96 B04
IN HAVELUND, S; KAARSHOLM, N; KAARSHOLM, N C
PA (NOVO) NOVO NORDISK AS; (NOVO) NOVO-NORDISK AS
CYC 91
PI WO 2000029013 A1 20000525 (200033)* EN 22p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
AU 2000012634 A 20000605 (200042)
EP 1131089 A1 20010912 (200155) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2002529514 W 20020910 (200274) 27p
US 6489292 B1 20021203 (200301)
ADT WO 2000029013 A1 WO 1999-DK627 19991116; AU 2000012634 A AU 2000-12634 19991116; EP 1131089 A1 EP 1999-955841 19991116, WO 1999-DK627 19991116; JP 2002529514 W WO 1999-DK627 19991116, JP 2000-582059 19991116; US

6489292 B1 Provisional US 1998-110707P 19981203, US 1999-441702 19991116
FDT AU 2000012634 A Based on WO 2000029013; EP 1131089 A1 Based on WO 2000029013; JP 2002529514 W Based on WO 2000029013
PRAI DK 1998-1506 19981118
TECH UPTX: 20000712
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred stabilizer: The stabilizer is isopinocampheol, 2,3-pinandiol, myrtanol, borneol, norborneol, fenchol, 1-adamantol, purine, adenine, guanine or hypoxanthine. The formulations may also comprise 3-150mM zwitterionic amine, e.g. glycyl-glycine, glycine, BICINE, TRICINE, BIS-TRIS or Good's buffers, and 5-50mM trishydroxymethylaminomethan.
Preferred formulation: The formulation contains at least 3 non-phenolic molecules, per six molecules of **insulin**, preferably upto 50mM of the non-phenolic substance. The formulation contains 0.3-20mM, preferably 0.6-15, especially 3-15mM human **insulin** or its analog, less than 50, preferably less than 10mM chloride, less than 10mM anions other than chloride or acetate, upto 5mM phosphate, and 2.0-4.5, preferably 2.5-3.5 Zn2+ ions, per six molecules of human **insulin**.

TECHNOLOGY FOCUS - POLYMERS - Preferred composition: The compositions may further comprise 0.001-1%, by weight, surfactant e.g. Tween 20 (RTM) or Poloxamer 188 (RTM).

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred analog: The analogs may be human **insulin** in which position B28 is Asp, Lys, Leu, Val or Ala, and position B29 is Lys or Pro; or des(B28-B30), des(B27) or des(B30 human **insulin**. The **insulin** derivative may be e.g. B29-Nepsilon-myristol-des(B30) human **insulin**, B29-Nepsilon-palmitoyl-des(B30) human **insulin**, B29-Nepsilon-myristoyl human **insulin**, B29-Nepsilon-myristol human **insulin**, B29-Nepsilon-palmitoyl human **insulin**, B28-Nepsilon-myristoyl LysB28ProB29 human **insulin**, B28-Nepsilon-palmitoyl LysB28 ProB29 human **insulin**, B30-Nepsilon-myristoyl-ThrB29 LysB30 human **insulin**, B30-Nepsilon-palmitoyl-ThrB29 LysB30 human **insulin**, B29-Nepsilon-(N-palmitoyl-gamma-glutamyl)-des(B30) human **insulin**, B29-Nepsilon-(N-**lithocholyl**-gamma-glutamyl)-des(B30) human **insulin**, B29-Nepsilon-(omega-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-Nepsilon-(omega-carboxyheptadecanoyl) human **insulin**.

L10 ANSWER 23 OF 28 USPATFULL on STN DUPLICATE 1
AN 1999:50875 USPATFULL
TI Crystallization of proteins
IN Balschmidt, Per, Esperg.ae butted.de, Denmark
Whittingham, Jean Lesley, York, United Kingdom
PA Novo Nordisk A/S, Bagsv.ae butted.rd, Denmark (non-U.S. corporation)
PI US 5898067 19990427
AI US 1998-17085 19980202 (9)
PRAI DK 1997-140 19970207
US 1997-38458P 19970220 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Russel, Jeffrey E.
LREP Zelson, Esq., Steve T., Green, Esq., Reza, Gregg, Esq., Valeta
CLMN Number of Claims: 28
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 443
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM In another preferred embodiment, the protein derivative is an **insulin** derivative selected from the group comprising

N.sup.εB29 -(myristoyl)des(B30) human **insulin**,
N.sup.εB29 -(myristoyl) human **insulin**,
N.sup.εB29 -(palmitoyl) human **insulin**,
N.sup.εB28 -(myristoyl)LyS.sup.B28 Pro.sup.B29 human
insulin, N.sup.εB28 -(palmitoyl)LyS.sup.B28 Pro.sup.B29
human **insulin**, N.sup.εB30 -(myristoyl)Thr.sup.B29
LyS.sup.B30 human **insulin**, N.sup.εB30
-(palmitoyl)Thr.sup.B29 Lys.sup.B30 human **insulin**,
N.sup.εB29 -(N-palmitoyl-γ-glutamyl)des(B30) human
insulin, N.sup.εB29 -(N- **lithocholyl**
-γ-glutamyl)des(B30) human **insulin** and
N.sup.εB29 -(w-carboxyheptadecanoyl)des(B30) human
insulin.

DETD Crystallization of N.sup.εB29 -(N- **lithocholyl**
-γ-glutamyl)des(B30) human **insulin**.

DETD The crystallization procedure according to Example 1 was repeated with use of N.sup.εB29 -(N- **lithocholyl**-γ-glutamyl)des(B30) human **insulin** in place of N.sup.εB29 -(myristoyl)des(30) human **insulin**.

CLM What is claimed is:
3. The method of claim 1 wherein the protein derivative is an **insulin** derivative selected from the group consisting of N.sup.εB29 -(myristoyl)des(B30) human **insulin**, N.sup.εB29 (myristoyl) human **insulin**, N.sup.εB29 -(palmitoyl) human **insulin**, N.sup.εB28 -(myristoyl)Lys.sup.B28 Pro.sup.B29 human **insulin**, N.sup.B28 -(palmitoyl)LyS.sup.B28 Pro.sup.B29 human **insulin**, N.sup.εB30 -(myristoyl)Thr.sup.B29 LyS.sup.B30 human **insulin**, N.sup.εB30 -(palmitoyl)Thr.sup.B29 Lys.sup.B30 human **insulin**, N.sup.εB29 -(N-palmitoyl-γ-glutamyl)des(B30) human **insulin**, N.sup.εB29 -(N- **lithocholyl**-γ-glutamyl)des(B30) human **insulin** and N.sup.εB29 -(ω-carboxyheptadecanoyl)des(B30) human **insulin**.

L10 ANSWER 24 OF 28 USPATFULL on STN
AN 1999:106427 USPATFULL
TI X14-mannitol
IN Kimer, Lone L.o slashed.gstrup, Farum, Denmark
Balschmidt, Per, Esperg.ae butted.rde, Denmark
Jensen, Steen, Drag.o slashed.r, Denmark
PA Novo Nordisk A/S, Bagsvaerd, Denmark (non-U.S. corporation)
PI US 5948751 19990907
AI US 1997-879691 19970619 (8)
PRAI DK 1996-684 19960620
DK 1996-899 19960827
US 1996-23264P 19960629 (60)
US 1996-24862P 19960828 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Lee, Howard C.
LREP Zelson, Esq., Steve T., Green, Esq., Reza
CLMN Number of Claims: 59
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 835
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD B29-N.sup.ε -myristoyl-des(B30)-human **insulin**,
B29-N.sup.ε -myristoyl human **insulin**,
B29-N.sup.ε -palmitoyl human **insulin**,

B28-N.sup.ε -myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε -palmitoyl Ly.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε -myristoyl-Thr.sup.B29 Lys.sup.B30 -human **insulin**, B30-N.sup.ε -palmitoyl-Thr.sup.B29 Lys.sup.B30 -human **insulin**, B29-N.sup.ε -(N-palmitoyl-γ-glutamyl)-des(B30)-human **insulin**, B29-N.sup.ε -(N- **lithocholyl** -γ-glutamyl)-des(B30)-human **insulin** and B29-N.sup.ε -(ω-carboxyheptadecanoyl)-des(B30)-human **insulin**; the most preferred being B29-N.sup.ε -myristoyl-des(B30)-human **insulin**.

CLM What is claimed is:

14. The **insulin** preparation of claim 1, wherein said derivative of human **insulin** is selected from the group consisting of: B29-N.sup.ε -myristoyl-des(B30)-humaninsulin, B29-N.sup.ε -myristoylhumaninsulin, B29-N.sup.ε -palmitoyl human **insulin**, B28-N.sup.ε -myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε -palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε -myristoyl-Thr.sup.B29 Lys.sup.B30 -human **insulin**, B30-N.sup.ε -palmitoyl-Thr.sup.B29 Lys.sup.B30 -human **insulin**, B29-N.sup.ε -(N-palmitoyl-γ-glutamyl)-des(B30-human **insulin**, B29-N.sup.ε -(N-**lithocholyl**-γ-glutamyl)-des(B30)-human **insulin** and B29-N.sup.ε -(ω-carboxyheptadecanoyl)-des(B30)-human **insulin**.

L10 ANSWER 25 OF 28 USPATFULL on STN
AN 1999:50836 USPATFULL
TI Method for producing powder formulation comprising an insulin
IN Jensen, Steen, Drag.o slashed.r, Denmark
Hansen, Philip, Holte, Denmark
PA Novo Nordisk A/S, Bagsvaerd, Denmark (non-U.S. corporation)
PI US 5898028 19990427
AI US 1998-45316 19980320 (9)
PRAI DK 1997-319 19970320
US 1997-41648P 19970327 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Russel, Jeffrey E.
LREP Zelson, Esq., Steve T., Green, Esq., Reza, Gregg, Esq., Valeta A.
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 434
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM The **insulin** derivative is most preferably selected from the group consisting of B29-N.sup.ε -myristoyl-des(B30) human **insulin**, B29-N.sup.ε -palmitoyl-des(B30) human **insulin**, B29-N.sup.ε -myristoyl human **insulin**, B29-N.sup.ε -palmitoyl human **insulin**, B28-N.sup.ε -myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε -palmitoyl LyS.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε -myristoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B30-N.sup.ε -palmitoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B29-N.sup.ε -(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.68 -(N-**lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε -(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε -(ω-carboxyheptadecanoyl) human

insulin.

L10 ANSWER 26 OF 28 USPATFULL on STN
AN 1999:15892 USPATFULL
TI Insulin preparations containing NaCl
IN Norup, Elsebeth, Jyllinge, Denmark
Langkj.ae butted.r, Liselotte, Klampenborg, Denmark
Havelund, Svend, Bagsvaerd, Denmark
PA Novo Nordisk A/S, Bagsvaerd, Denmark (non-U.S. corporation)
PI US 5866538 19990202
AI US 1997-879991 19970620 (8)
PRAI DK 1996-685 19960620
US 1996-20927P 19960627 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Tsang, Cecilia J.; Assistant Examiner: Borin, Michael
LREP Zelson, Esq., Steve T., Green, Esq., Reza, Rozek, Esq., Carol E.
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 467
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM B29-N.sup.ε -myristoyl-des(B30) human **insulin**, B29-N.sup.ε -palmitoyl-des(B30) human **insulin**, B29-N.sup.ε -myristoyl human **insulin**, B29-N.sup.ε -palmitoyl human **insulin**, B28-N.sup.ε -myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε -palmitoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε -myristoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B30-N.sup.ε -palmitoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B29-N.sup.ε -(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε -(N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin** and B29-N.sup.ε -(ω-carboxyheptadecanoyl)-des(B30) human **insulin**, B29-N.sup.ε -(ω-carboxyheptadecanoyl) human **insulin**; the most preferred being B29-N.sup.ε -myristoyl-des(B30) human **insulin**.

CLM What is claimed is:
9. A pharmaceutical formulation according to claim 8, wherein the **insulin** derivative is selected from the group consisting of B29-N.sup.ε -myristoyl-des(B30) human **insulin**, B29-N.sup.ε -palmitoyl-des(B30) human **insulin**, B29-N.sup.ε -myristoyl human **insulin**, B29-N.sup.ε -palmitoyl human **insulin**, B28-N.sup.ε -myristoyl Lys.sup.B28 Pro.sup.B29 human **insulin**, B28-N.sup.ε -palmitoyl-Lys.sup.B28 Pro.sup.B29 human **insulin**, B30-N.sup.ε -myristoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B30-N.sup.ε -palmitoyl-Thr.sup.B29 Lys.sup.B30 human **insulin**, B29-N.sup.ε -(N-palmitoyl-γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε (N- **lithocholyl** -γ-glutamyl)-des(B30) human **insulin**, B29-N.sup.ε -(ω-carboxyheptadecanoyl)-des(B30) human **insulin** and B29-N.sup.ε -(ω-carboxyheptadecanoyl) human **insulin**.

L10 ANSWER 27 OF 28 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1999-458253 [38] WPIDS

DNC C1999-134508
TI Stabilized parenteral insulin compositions.
DC B04
IN LANGBALLE, P; NORUP, E
PA (NOVO) NOVO-NORDISK AS; (NOVO) NOVO NORDISK AS
CYC 85
PI WO 9934821 A1 19990715 (199938)* EN 30p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
AU 9918700 A 19990726 (199952)
EP 1044016 A1 20001018 (200053) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6174856 B1 20010116 (200106)
JP 2002500196 W 20020108 (200206) 34p
ADT WO 9934821 A1 WO 1999-DK6 19990106; AU 9918700 A AU 1999-18700 19990106; EP 1044016 A1 EP 1999-900206 19990106, WO 1999-DK6 19990106; US 6174856 B1 Provisional US 1998-71336P 19980114, US 1999-227053 19990107; JP 2002500196 W WO 1999-DK6 19990106, JP 2000-527269 19990106
FDT AU 9918700 A Based on WO 9934821; EP 1044016 A1 Based on WO 9934821; JP 2002500196 W Based on WO 9934821
PRAI EP 1998-610001 19980109
TECH UPTX: 19990922
TECHNOLOGY FOCUS - PHARMACEUTICALS - The buffer is Gly-Gly present in an amount of 1-20 (preferably 4-10) mM. The composition contains 0.1-10 (preferably 2-3) metal ions per hexamer of **insulin**, the metal ions being preferably calcium. In the human **insulin** analog, the amino acid residue at position B28 is Leu, Val or Ala, but preferably Asp or Lys, and at position B29 it is Lys or Pro; or the analog is des(B28-B30), des(B27) or des(B30) human **insulin**. The **insulin** derivative is an acylated **insulin** e.g. an **insulin** derivative where the epsilon-amino group of LysB29 contains an acyl substituent comprising at least 6 carbon atoms. The **insulin** derivative is preferably NepsilonB29-myristoyl-des(B30) human **insulin**, NepsilonB29-palmitoyl-des(B30) human **insulin**, NepsilonB29-myristoyl human **insulin**, NepsilonB29-palmitoyl human **insulin**, NepsilonB28-myristoyl-LysB28ProB28 human **insulin**, NepsilonB29-palmitoyl-LysB28ProB28 human **insulin**, NepsilonB30-myristoyl-ThrB29LysB30 human **insulin**, NepsilonB29-palmitoyl-ThrB29LysB30 human **insulin**, NepsilonB29-(N-palmitoyl-gamma-glutamyl)-des(B30) human **insulin**, NepsilonB29-(N-**lithocholyl**-gamma-glutamyl)-des(B30) human **insulin**, NepsilonB29-(omega-carboxyheptadecanoyl)-des(B30) human **insulin** or NepsilonB29-(omega-carboxyheptadecanoyl) human **insulin**, especially NepsilonB29-myristoyl-des(B30) human **insulin**.

L10 ANSWER 28 OF 28 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1998-594469 [50] WPIDS
DNC C1998-178264
TI New zinc free insulin crystals for pulmonary administration - optionally contain phenolic stabiliser and carbohydrate carrier.
DC B04 B07
IN HAVELUND, S
PA (NOVO) NOVO NORDISK AS; (NOVO) NOVO-NORDISK AS; (HAVE-I) HAVELUND S
CYC 82
PI WO 9842749 A1 19981001 (199850)* JA 21p
RW: AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

AU 9866120 A 19981020 (199909)
NO 9904520 A 19990917 (200001)
CZ 9903209 A3 20000315 (200021)
EP 1005490 A1 20000607 (200032) EN
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MK NL PT RO SE SI
BR 9808285 A 20000516 (200035)
CN 1259142 A 20000705 (200052)
HU 2000000547 A2 20000828 (200055)
MX 9908401 A1 20000401 (200124)
JP 2001506272 W 20010515 (200133) 21p
KR 2000076419 A 20001226 (200134)
US 2001039260 A1 20011108 (200171)
US 6310038 B1 20011030 (200172)
AU 742591 B 20020110 (200217)
US 2002198140 A1 20021226 (200304)
RU 2198181 C2 20030210 (200324)

ADT WO 9842749 A1 WO 1998-DK109 19980320; AU 9866120 A AU 1998-66120 19980320; NO 9904520 A WO 1998-DK109 19980320, NO 1999-4520 19990917; CZ 9903209 A3 WO 1998-DK109 19980320, CZ 1999-3209 19980320; EP 1005490 A1 EP 1998-907916 19980320, WO 1998-DK109 19980320; BR 9808285 A BR 1998-8285 19980320, WO 1998-DK109 19980320; CN 1259142 A CN 1998-805938 19980320; HU 2000000547 A2 WO 1998-DK109 19980320, HU 2000-547 19980320; MX 9908401 A1 MX 1999-8401 19990913; JP 2001506272 W JP 1998-544747 19980320, WO 1998-DK109 19980320; KR 2000076419 A WO 1998-DK109 19980320, KR 1999-708523 19990918; US 2001039260 A1 Provisional US 1997-41390P 19970327, Cont of US 1998-45038 19980320, US 2001-836496 20010417; US 6310038 B1 Provisional US 1997-41390P 19970327, US 1998-45038 19980320; AU 742591 B AU 1998-66120 19980320; US 2002198140 A1 Provisional US 1997-41390P 19970327, Cont of US 1998-45038 19980320, Cont of US 2001-836496 20010417, US 2002-152535 20020520; RU 2198181 C2 WO 1998-DK109 19980320, RU 1999-122036 19980320

FDT AU 9866120 A Based on WO 9842749; CZ 9903209 A3 Based on WO 9842749; EP 1005490 A1 Based on WO 9842749; BR 9808285 A Based on WO 9842749; HU 2000000547 A2 Based on WO 9842749; JP 2001506272 W Based on WO 9842749; KR 2000076419 A Based on WO 9842749; AU 742591 B Previous Publ. AU 9866120, Based on WO 9842749; US 2002198140 A1 Cont of US 6310038; RU 2198181 C2 Based on WO 9842749

PRAI DK 1997-317 19970320

AB WO 9842749 A UPAB: 19981217

Zinc free **insulin** crystals (ZFIC) having a diameter of <10 mu m are new. Also claimed are (i) a therapeutic powder formulation suitable for pulmonary administration comprising the above ZFIC; and (ii) a method of treating diabetes mellitus comprising pulmonary delivery of an **insulin** derivative having a protracted onset of action, preferably selected from B29-N(epsilon)-myristoyl-des(B30), B29-N(epsilon)-palmitoyl-des(B30), B29-N(epsilon)-myristoyl, B29-N(epsilon)-palmitoyl, B28-N(epsilon)-myristoyl-Lys(B28) Pro(B29), B28-N(epsilon)-palmitoyl-Lys(B28) Pro(B29), B30-N(epsilon)-myristoyl-Thr(B29) Lys(B30), B30-N(epsilon)-palmitoyl-Thr(B29) Lys(B30), B29-N(epsilon)-(N-palmitoyl-gamma -glutamyl)-des(B30), B29-N(epsilon)-(N-**lithocholyl**- gamma -glutamyl)-des(B30), B29-N(epsilon)-(-carboxyheptadecanoyl)-des(B30) or B29-N(epsilon)-(-carboxyheptadecanoyl) -human **insulin**.

USE - The ZFIC can be used administered to the lungs for the treatment of diabetes mellitus.

ADVANTAGE - The crystals have reduced tendency to associate into aggregates in the dry powder. Pulmonary administration avoids the need to inject **insulin**.

Dwg.0/1